

REMARKS

Applicant respectfully requests reconsideration. Claims 1-12 and 14-19 were previously pending in this application with claims 1-12 and 14 withdrawn from consideration. By this amendment, Applicant is canceling claims 1-12 and 14 without prejudice or disclaimer to advance prosecution. Applicant reserves the right to file one or more continuing applications directed to the subject matter of the canceled claims. As a result claims 15-19 are pending.

Claim 15 has been amended to advance prosecution. Support for the amendment to claim 15 may be found in claim 15 as filed, on page 6, line 8, and on page 6, lines 6-10. No new matter has been added.

Applicant acknowledges withdrawal of the previous rejections of record under 35 U.S.C. §112 and the rejections under 35 U.S.C. §103 over Araki et al., in view of Blomberg et al. and Grimble R. F. in view of Sammon and “any rejection not specifically stated in this Office Action”.

Rejections under 35 U.S.C. §112

Claims 15-16 and 19 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the “Applicant has not provided a description of the structure of a representative number of derivatives of riboflavin nor a description of the chemical and /or physical characteristics of a representative number of such derivatives nor a description of how to obtain a representative number of specific derivatives.”

Without conceding to the merits of the Examiner’s position, claim 15 has been amended to recite specific derivatives of riboflavin.

In view of the above amendments withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections Under 35 U.S.C. §103

Claims 15-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble RF (Effect of antioxidative vitamins on immune function with clinical applications. Internat. J. Vit. Nutr. Res. (1997); 67(5):312-20). The Examiner alleges that Grimble teaches that “antioxidative

vitamins *such as riboflavin* prevent increased cytokine production *via the glutathione production pathway.*" (citing the abstract ("Summary") in Grimble – Emphasis added). According to the Examiner, "one of ordinary skill in the art would have found it obvious that a reduction in cytokines would be efficacious in the treatment of hypercytokinemia." The Examiner also alleges that "[t]he use of a salt of riboflavin would have been obvious to one of ordinary skill in the art since salts dissociate and a salt of riboflavin would naturally dissociate into riboflavin and the salt." The Examiner further asserts that "to treat a patient, one would need to administer the riboflavin and such as claimed in claim 19 would have been obvious to one of ordinary skill in the art." The Examiner concludes that Grimble "teaches and makes prima facie obvious how to use the claimed invention at the time that it was made."

The Examiner considered Applicant's arguments filed on June 22, 2006 but did not find them to be persuasive. According to the Examiner "Grimble need not teach how or via what mechanism of action riboflavin has on cytokine levels, jut that there is a decrease therein which is further taught in the diagram on page 317 as well as in the body of the reference." Applicant respectfully disagrees with the Examiner and traverses the rejection. Grimble does not teach that *antioxidative vitamins such as riboflavin* prevent increased cytokine production via the *glutathione production pathway.* The "Summary" in Grimble recites (Emphasis added):

"The antioxidative vitamins, ascorbic acid and the tocopherols, are important not only for limiting tissue damage but also in preventing increased cytokine production which is a consequence of excessive activation of NFκB."

The antioxidant vitamins taught by Grimble to prevent increased cytokine production are ascorbic acid and the tocopherols. Grimble does not teach or even suggest that riboflavin prevents increased cytokine production as asserted by the Examiner.

Applicant disagrees with the Examiner's interpretation of Figure 4 on page 317, namely in that it teaches that riboflavin decreases cytokines. The text which references Figure 4 (starting in the right column on page 317 through the left column on page 318) recites (Emphasis added):

"The interaction between the response of the immune system to pathogens and inflammatory agents, and antioxidative vitamins is

complex. However two common themes emerge amid the complexity (Fig. 4).

The first of these is the influence of antioxidant defense upon the immune response. *Inflammatory aspects of the response will be changed in their intensity by the extent of release of inflammatory mediators into extracellular compartments of the body and by the extent of activation of transcription factors, such as NFκB, at the intracellular level.* Poor antioxidant defences, or enhanced antioxidant production, will increase the intensity of these events and hence the extent of the inflammatory response. *Increased intakes of vitamin C and E will counteract this effect.* Immune aspects of the response will also be influenced by the extent of the inflammatory response since prostaglandins which are products of the response, are immunosuppressive in nature. Thus enhanced inflammation may exert immunosuppressive effects. Vitamin E may thus also influence the response of the immune system by suppression of prostaglandin production during the inflammatory response.

The second of the themes may relate to intracellular glutathione concentrations. The molecule acting in its role as an antioxidant and as a modulator of the interaction between NFκB and DNA within lymphocytes and other cells. *Likewise vitamins which have no direct antioxidative properties but which influence glutathione metabolism, may exert a modulatory role. Such vitamins are riboflavin, which is an important co-factor for glutathione reductase and vitamin B₆ which is important in the synthetic pathway for cysteine, the rate limiting precursor for glutathione synthesis."*

The above text clearly teaches that vitamin C (ascorbic acid) and vitamin E (tocopherol) are important in preventing increased cytokine production and that riboflavin (which has "no direct antioxidative properties") may exert a modulatory role on the inflammatory response by acting as a cofactor for glutathione reductase. There is no teaching or suggestion from the above that Figure 4 teaches or suggests that riboflavin decreases cytokine production.

Applicant has thoroughly reviewed the Grimble reference and, contrary to the Examiner's assertion, did not find any teaching or suggestion in the entire reference that riboflavin decreases cytokines.

Grimble's teaching of the role of riboflavin is summarized on page 317 left column, 2nd full paragraph: "[r]iboflavin is an important cofactor in glutathione metabolism because of its role as a cofactor for glutathione reductase. However, whether this role is responsible for the influence of the vitamin on immune function is unclear." The only examples in Grimble of the

effects of a lack of riboflavin are: a decrease in lymphocytes, decreased thymus weight, and a decreased antibody response. Thus, Grimbale does not teach or suggest any relationship between riboflavin and cytokines.

Applicant also disagrees with the Examiner's assertion that Grimbale teaches that the antioxidative vitamins prevent increased cytokine production *via the glutathione production pathway*. As stated above, Grimbale clearly teaches that the antioxidative vitamins, ascorbic acid and the tocopherols, prevent increased cytokine production *via NFκB* and not via the glutathione production pathway (see "Summary" (abstract) and page 317 in Grimbale). Furthermore, Grimbale does not teach or suggest that riboflavin is involved in regulating the NFκB pathway which regulates cytokine production. Accordingly, Grimbale does not teach and cannot suggest the regulation of cytokine production via riboflavin.

Therefore, Grimbale does not teach, suggest or even provide the motivation for one of ordinary skill in the art to use riboflavin to reduce cytokines let alone teach or suggest using riboflavin to treat hypercytokinemia.

In view of the above arguments, withdrawal of the rejection of the claims under 35 U.S.C. §103, is respectfully requested.

Double Patenting Rejection

The Examiner provisionally rejected claims 15-19 under the judicially created doctrine of obviousness-type double patenting over claim 1-20 of co-pending US application 10/472621. Without conceding to the merits of the Examiner's position, Applicants defer substantive rebuttal until the conflicting claims of the above-identified co-pending applications have been allowed.

If the provisional double patenting rejection is the only rejection remaining, the Examiner is kindly requested to withdraw the rejection in the instant application and permit the application to issue as a patent (see MPEP § 804).

Serial No.: 10/506631
Confirmation No.: 5167

- 8 -

Art Unit: 1614

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Araki et al., Applicant

By: 

Roque El-Hayek, Reg. No. 55,151
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: T0509.70011US00
Date: December 27, 2006
x01/05/07x